

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

**PCT**

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 11 April 2001 (11.04.01)	
International application No. PCT/US00/40446	Applicant's or agent's file reference MAR618/4005A
International filing date (day/month/year) 21 July 2000 (21.07.00)	Priority date (day/month/year) 22 July 1999 (22.07.99)
Applicant GAYED, Atef	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
20 February 2001 (20.02.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafla Telephone No.: (41-22) 338.83.38
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number  
**WO 01/07075 A3**

- (51) International Patent Classification<sup>7</sup>: **A61K 38/18**, 47/18, 47/10
- (74) Agent: **DAVIES, Tracey, B.**; Vinson & Elkins L.L.P., 2300 First City Tower, 1001 Fannin, Houston, TX 77002-6760 (US).
- (21) International Application Number: **PCT/US00/40446**
- (22) International Filing Date: **21 July 2000 (21.07.2000)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:  
60/198,216                      22 July 1999 (22.07.1999)    **US**
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:  
**US**    09/359,949 (CON)  
Filed on                                      22 July 1999 (22.07.1999)
- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (71) Applicant (*for all designated States except US*): **AVENTIS PHARMACEUTICALS, INC.** [US/US]; Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807 (US).
- (88) Date of publication of the international search report:  
4 October 2001
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **GAYED, Atef** [US/US]; 4820 W. 121st. Street, Overland Park, KS 66209 (US).
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **MULTI-DOSE ERYTHROPOIETIN FORMULATIONS**

(57) Abstract: The present invention is directed to multi-dose erythropoietin formulations for parenteral administrations. The formulations contain one or more of the following preservatives benzethonium chloride, phenoxyethanol and phenylethyl alcohol.

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/40446

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>EP 0 459 795 A (KIRIN-AMGEN, INC.) 4 December 1991 (1991-12-04)</p> <p>page 4, line 45 - line 49 -----</p>	<p>1,4-8, 16-19, 35, 38-42, 50-54, 57-61, 69-72</p>

# INTERNATIONAL SEARCH REPORT

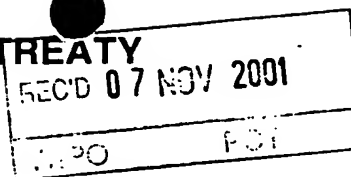
International Application No

PCT/US 00/40446

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 199992	A	05-11-1986	JP 1922237 C	07-04-1995
			JP 6051637 B	06-07-1994
			JP 61221125 A	01-10-1986
			AT 55912 T	15-09-1990
			CA 1269205 A	22-05-1990
			DE 3673685 D	04-10-1990
US 5045529	A	03-09-1991	AT 117805 T	15-02-1995
			CA 2049970 A	28-09-1990
			DE 69016415 D	09-03-1995
			DE 69016415 T	08-06-1995
			EP 0465510 A	15-01-1992
			JP 2938566 B	23-08-1999
			JP 4504306 T	30-07-1992
			WO 9011527 A	04-10-1990
			US 5558985 A	24-09-1996
			US 5320965 A	14-06-1994
			US 5304491 A	19-04-1994
US 5503827	A	02-04-1996	DE 4126983 A	18-02-1993
			AT 145138 T	15-11-1996
			AU 710768 B	30-09-1999
			AU 1633997 A	22-05-1997
			AU 678756 B	12-06-1997
			AU 2409492 A	16-03-1993
			CA 2115348 A	04-03-1993
			CZ 284853 B	17-03-1999
			CZ 9400287 A	17-08-1994
			DE 59207523 D	19-12-1996
			DK 607156 T	07-04-1997
			WO 9303744 A	04-03-1993
			EP 0528313 A	24-02-1993
			EP 0607156 A	27-07-1994
			ES 2094923 T	01-02-1997
			FI 940674 A	14-02-1994
			GR 3022037 T	31-03-1997
			HU 67379 A	28-04-1995
			IL 102775 A	22-12-1999
			JP 6510031 T	10-11-1994
			MX 9204636 A	01-02-1993
			NO 940499 A	14-02-1994
			RU 2091068 C	27-09-1997
			SG 66226 A	20-07-1999
			SK 14894 A	09-11-1994
			ZA 9206122 A	14-02-1994
EP 459795	A	04-12-1991	JP 4253919 A	09-09-1992
			DE 69104777 D	01-12-1994
			EP 0459516 A	04-12-1991
			US 5597562 A	28-01-1997

# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MAR618/4005A</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US00/40446</b>	International filing date (day/month/year) <b>21/07/2000</b>	Priority date (day/month/year) <b>22/07/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K38/18</b>		
Applicant <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  <b>20/02/2001</b>	Date of completion of this report  <b>02.11.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Langer, A</b>  Telephone No. +49 89 2399 7809  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40446

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-19 as originally filed

**Claims, No.:**

1-72 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40446

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:  
**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19, 22, 25, 27, 30-33, 35-72
	No:	Claims	20, 21, 23, 24, 26, 28, 29, 34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-72
Industrial applicability (IA)	Yes:	Claims	1-72
	No:	Claims	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/40446

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2. Citations and explanations  
**see separate sheet**



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

**Re Item IV**

Lack of unity of invention

The separate groups of invention are:

1. Claims 1-19, 35-72:      Pharmaceutical compositions comprising benzethonium chloride as preservative and methods for their manufacture.
2. Claims 20-34:      Carrier compositions comprising benzethonium chloride in concentrations effective to inhibit bacterial growth.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Carriers comprising benzethonium chloride in concentrations effective to inhibit bacterial growth are known in the art (document D2). Furthermore, it is known, that benzethonium chloride can be used as preservative (document D5). The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of inventions indicated.

The applicant was not invited to pay additional fees as all claims could be examined without any additional effort justifying the payment of additional fees.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.      Reference is made to the following documents. If not indicated otherwise, the relevant passages are those cited in the international search report.

D1: EP-A-0 199 992 (EISAI CO.,LLTD.) 5 November 1986 (1986-11-05)

D2: US-A-5 045 529 (CHIANG) 3 September 1991 (1991-09-03)

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

additional relevant passage: column 6

D3: US-A-5 503 827 (WOOG ET AL.) 2 April 1996 (1996-04-02) cited in the application

D4: EP-A-0 459 795 (KIRIN-AMGEN, INC.) 4 December 1991 (1991-12-04)

D5: DURIEUX ET AL: 'Synergistic inhibition of muscarinic signalling by ketamine stereoisomer and the preservative benzethonium chloride', ANESTHESIOLOGY, , 1997, vol. 86, no. 6, pages 1326 to 1333, abstract

The document D5 was not cited in the international search report. A copy of the document is appended hereto.

**2. Novelty (Art. 33 (2) PCT)**

The features of **claims 20, 23, 24, 34** are disclosed by documents D1 and D2, while **claims 21, 28, 29** are disclosed by document D2 and **claim 26** is disclosed by document D1.

These claims therefore lack novelty in terms of Art. 33 (2) PCT.

The features of claims 1-19, 22, 25, 27, 30-33, 35-72 are not disclosed by the prior art cited and therefore appear novel in terms of Art. 33 (2) PCT.

**3. Inventive Step (Art. 33 (3) PCT)**

**Claims 20, 21, 23, 24, 26, 28, 29, 34**, which are not novel in terms of Art. 33 (2) PCT, also lack inventive skill in terms of Art. 33 (3) PCT.

The use of benzethonium chloride as preservative is known in the art (document D5). Its use as additive in compositions comprising erythropoietin is also known (document D4). Document D3 discloses the use of preservatives in erythropoietin compositions. It would therefore be obvious for the skilled person to use benzethonium chloride in erythropoietin compositions. Independent **claims 1, 35, 54** are therefore not inventive in terms of Art. 33 (3) PCT.

In view of the prior art, the additional features of the dependent claims **2-19, 22,**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

**25, 27, 30-33, 36-53, 55-72** are not considered to involve inventive skill in terms of Art. 33 (3) PCT.

**4. Industrial Applicability (Art. 33 (4) PCT)**

**Claims 1-72** fulfil the criteria of industrial applicability as laid down in Art. 33 (4) PCT.

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PERRY, Robert  
GILL JENNINGS & EVERY  
Broadgate House  
7 Eldon Street  
GB-EC2M 7LH London  
GRANDE BRETAGNE

RECEIVED

5 NOV 2001

02.11.2001

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing

(day/month/year)

02.11.2001

Applicant's or agent's file reference

MAR618/4005A

IMPORTANT NOTIFICATION

International application No.

PCT/US00/40446

International filing date (day/month/year)

21/07/2000

Priority date (day/month/year)

22/07/1999

Applicant

AVENTIS PHARMACEUTICALS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Ferro Vasconcelos, M

Tel. +49 89 2399-7006

8042




# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MAR618/4005A</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) <b>FOR FURTHER ACTION</b>	
International application No. <b>PCT/US00/40446</b>	International filing date (day/month/year) <b>21/07/2000</b>	Priority date (day/month/year) <b>22/07/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K38/18</b>		
Applicant <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.  2. This REPORT consists of a total of 7 sheets, including this cover sheet.  <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  These annexes consist of a total of    sheets.		
3. This report contains indications relating to the following items:  <div style="margin-left: 40px;">           I    <input checked="" type="checkbox"/> Basis of the report            II   <input type="checkbox"/> Priority            III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability            IV   <input checked="" type="checkbox"/> Lack of unity of invention            V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement            VI   <input type="checkbox"/> Certain documents cited            VII <input type="checkbox"/> Certain defects in the international application            VIII <input type="checkbox"/> Certain observations on the international application         </div>		
Date of submission of the demand  <b>20/02/2001</b>	Date of completion of this report  <b>02.11.2001</b>	
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  <b>Langer, A</b>  Telephone No. +49 89 2399 7809	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/4044:

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-19 as originally filed

**Claims, No.:**

1-72 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/4044

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3

- ☐ complied with.
- ☒ not complied with for the following reasons:  
**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19, 22, 25, 27, 30-33, 35-72
	No:	Claims	20, 21, 23, 24, 26, 28, 29, 34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-72
Industrial applicability (IA)	Yes:	Claims	1-72
	No:	Claims	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/4044

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2. Citations and explanations  
**see separate sheet**



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

**Re Item IV**

Lack of unity of invention

The separate groups of invention are:

1. Claims 1-19, 35-72:      Pharmaceutical compositions comprising benzethonium chloride as preservative and methods for their manufacture.
2. Claims 20-34:      Carrier compositions comprising benzethonium chloride in concentrations effective to inhibit bacterial growth.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Carriers comprising benzethonium chloride in concentrations effective to inhibit bacterial growth are known in the art (document D2). Furthermore, it is known, that benzethonium chloride can be used as preservative (document D5). The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of inventions indicated.

The applicant was not invited to pay additional fees as all claims could be examined without any additional effort justifying the payment of additional fees.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents. If not indicated otherwise, the relevant passages are those cited in the international search report.

D1: EP-A-0 199 992 (EISAI CO.,LLTD.) 5 November 1986 (1986-11-05)

D2: US-A-5 045 529 (CHIANG) 3 September 1991 (1991-09-03)

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

additional relevant passage: column 6

D3: US-A-5 503 827 (WOOG ET AL.) 2 April 1996 (1996-04-02) cited in the application

D4: EP-A-0 459 795 (KIRIN-AMGEN, INC.) 4 December 1991 (1991-12-04)

D5: DURIEUX ET AL: 'Synergistic inhibition of muscarinic signalling by ketamine stereoisomer and the preservative benzethonium chloride', ANESTHESIOLOGY, , 1997, vol. 86, no. 6, pages 1326 to 1333, abstract

The document D5 was not cited in the international search report. A copy of the document is appended hereto.

**2. Novelty (Art. 33 (2) PCT)**

The features of **claims 20, 23, 24, 34** are disclosed by documents D1 and D2, while **claims 21, 28, 29** are disclosed by document D2 and **claim 26** is disclosed by document D1.

These claims therefore lack novelty in terms of Art. 33 (2) PCT.

The features of claims 1-19, 22, 25, 27, 30-33, 35-72 are not disclosed by the prior art cited and therefore appear novel in terms of Art. 33 (2) PCT.

**3. Inventive Step (Art. 33 (3) PCT)**

**Claims 20, 21, 23, 24, 26, 28, 29, 34**, which are not novel in terms of Art. 33 (2) PCT, also lack inventive skill in terms of Art. 33 (3) PCT.

The use of benzethonium chloride as preservative is known in the art (document D5). Its use as additive in compositions comprising erythropoietin is also known (document D4). Document D3 discloses the use of preservatives in erythropoietin compositions. It would therefore be obvious for the skilled person to use benzethonium chloride in erythropoietin compositions. Independent **claims 1, 35, 54** are therefore not inventive in terms of Art. 33 (3) PCT.

In view of the prior art, the additional features of the dependent claims **2-19, 22**,

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/40446

25, 27, 30-33, 36-53, 55-72 are not considered to involve inventive skill in terms of Art. 33 (3) PCT.

**4. Industrial Applicability (Art. 33 (4) PCT)**

**Claims 1-72** fulfil the criteria of industrial applicability as laid down in Art. 33 (4) PCT.

# PATENT COOPERATION T

From the INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:  
 Vinson & Elkins L.L.P.  
 Attn. Davies, T.  
 2300 First City Tower  
 1001 Fannin Street  
 Houston, Texas 77002-6760  
 UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT  
 OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference <b>MAR618/4005A</b>	Date of mailing (day/month/year) <b>18/04/2001</b>
International application No. <b>PCT/US 00/ 40446</b>	International filing date (day/month/year) <b>21/07/2000</b>
Applicant <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

**For more detailed instructions,** see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.


☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <b>Jaap Hurenkamp</b>
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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>MAR618/4005A</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 40446</b>	International filing date (day/month/year) <b>21/07/2000</b>	(Earliest) Priority Date (day/month/year) <b>22/07/1999</b>
Applicant <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/40446

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/18 A61K47/18 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 199 992 A (EISAI CO.,LLTD.) 5 November 1986 (1986-11-05) page 13, line 17 - line 20	20,23-27
Y	claims 1,3	21
Y	US 5 045 529 A (CHIANG) 3 September 1991 (1991-09-03) column 4, line 34 - line 42 column 7, line 34 - line 35	21
Y	US 5 503 827 A (WOOG ET AL.) 2 April 1996 (1996-04-02) cited in the application	1,4-8, 16-19, 35, 38-42, 50-54, 57-61, 69-72
	the whole document	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

3 April 2001

Date of mailing of the international search report

18/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Benz, K



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/40446

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 459 795 A (KIRIN-AMGEN, INC.) 4 December 1991 (1991-12-04)  page 4, line 45 - line 49 -----	1,4-8, 16-19, 35, 38-42, 50-54, 57-61, 69-72

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/40446

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			JP 6051637 B	06-07-1994
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			DE 69104777 D	01-12-1994
			EP 0459516 A	04-12-1991
			US 5597562 A	28-01-1997
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3	BIB	1

Total number of pages: 8

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